Machine learning modeling of intraoperative hemodynamic predictors of 30-day mortality and major in-hospital morbidity after noncardiac surgery: a retrospective population cohort study

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Lay summary

Introduction: The World Health Organization estimates that 270-360 million operations are performed every year worldwide. Death and complications after surgery are a big challenge. In Canada, out of every 1000 major surgeries, 16 patients die in hospital after surgery. In the United States, for every 1000 operations, 67 patients unexpectedly need life support in the Intensive Care Unit. With population aging and limited resources, strategies to improve health after surgery are ever more important.

Vital signs, such as blood pressure and heart rate, show how the body is doing. Vital signs change during surgery because of patient, surgical, and anesthetic factors. Anesthesiologists can change vital signs with medications. However, we are only starting to understand which, and what ranges of, vital signs under anesthesia are associated with better health. Machine learning is a tool that can provide new ways to understand data. With better understanding, we can work to improve outcomes after surgery.

Objective: We will analyze vital signs during surgeries for their links to death, complications (heart, lung, kidney, brain, infection), Intensive Care Unit admission, length of hospital stay, and hospital readmission. We will determine which, and what levels of, vital signs may be harmful. We predict that blood pressure, heart rate, oxygen level, carbon dioxide level, and the need for medications to change blood pressure will interact to be associated with death after surgery.

Methods: After obtaining Research Ethics Board approval, we will analyze data from all patients who are at least 45 years old and had an operation (with the exception of heart surgery) with an overnight stay at the QEII health centre from January 1, 2013 to December 1, 2017. There are approximately eligible 35,000 patients. We will use machine learning to model the data and test how well our model explains outcomes after surgery.

Significance: Our use of machine learning in a large, broad surgery population dataset could detect new relationships and strategies that may inform current practice, and generate ideas for future research. A better understanding of the impact of vital signs during surgeries may unveil methods to improve outcomes and resource allocation after surgery. The results may suggest ways to identify high-risk patients who should be monitored more closely after surgery. If our model performs well, it may motivate other researchers to use machine learning in health data research. The model we plan to develop will be based on information at the QEII, so it may be relevant to the care of Nova Scotians and beyond.

Protocol

Introduction

Surgical rates are increasing worldwide, with the World Health Organization estimating 270-360 million operations globally in 2012 (1). Surgical mortality and morbidity remain a significant concern. Worldwide, more than 4.2 million patients die within 30 days of surgery every year, accounting for 7.7% of the global deaths (2). In Canada 2016-2017, for every 1000 major surgeries performed, 16 patients die in hospital after surgery (3). Unplanned ICU admission occurred after 6.7% of non-cardiac surgeries in a large American cohort study (4). During the intraoperative period, there may be severe hemodynamic (vital sign) derangements (e.g. abnormalities in blood pressure, heart rate, and oxygen level) that could play a significant role in postoperative mortality. However, due to the quantity and complexity of perioperative data, the threshold for harm of potentially modifiable intraoperative hemodynamic factors remain incompletely understood. Using machine learning techniques, this study will investigate the impact of multiple hemodynamic variables in the perioperative context.

Background and significance

Postoperative outcomes result from a complex interplay of patient, surgical, and anesthetic factors. Several validated preoperative risk stratification scores exist, including the Revised Cardiac Risk Index (RCRI), Portsmouth-Physiology and Operative Severity Score for the enUmeration of Mortality (POSSUM), Surgical Risk Scale, and National Surgical Quality Improvement Program (NSQIP) (5–7). However, the derivation process of these models did not include intraoperative hemodynamic variables and thus may not be responsive to the impact of intraoperative hemodynamic derangements.

The Surgical Apgar Score (SAS) is a simple 10-point score involving intraoperative variables of estimated blood loss, blood pressure, and heart rate for composite mortality and morbidity. The SAS has varying predictive accuracy across surgical specialties (8,9) and its addition has not significantly improved preoperative risk prediction (10). Since the initial publication of the SAS in 2007 (11), there has been increasing interest in elucidating the role of intraoperative hemodynamics on mortality and morbidity, including hypotension (12,13), heart rate (14,15), anesthetic depth (16), end-tidal carbon dioxide (17) and oxygen saturation (18). A recent systematic review on hypotension found that due to heterogeneity and methodological limitations, one cannot conclude based on available evidence that intraoperative hypotension causes adverse outcomes (12). The impact of blood pressure perioperatively is physiologically complex, with factors including autoregulation, microvascular dysfunction, and limitations of measurement (19).

Our understanding of the impact of intraoperative hemodynamics remains limited as they have been mostly evaluated in isolation. The interactions between intraoperative hemodynamic variables have not been systematically evaluated for association with postoperative outcomes. Hemodynamics are a reflection of physiology, surgical stress, and medications. If found to be predictive of outcomes, automatically recorded hemodynamic variables could provide robust, objective risk stratification within intraoperative anesthesia information systems.

We would like to leverage machine learning to elucidate hemodynamic contributors in the perioperative surgical, physiologic and pharmacologic milieu in the non-cardiac surgery population. Machine learning refers to a set of advanced statistical techniques to evaluate the correlations and associations within large data sets (20). This includes logistic regression with

variable selection, where the most important predictors are chosen from a set of predictors to build a parsimonious model (21). Another machine learning technique is Principal Component Analysis (PCA), which finds groups of correlated predictors amongst a large set of potential predictors (i.e. dimensionality reduction) (21). The most important groups of predictors could then be placed in a model. Other modeling techniques we will use include classification trees, which predict outcomes based on input variables through classification, random forest to show which predictor has the highest importance, and association rule learning to help profiles of linked predictors (21).

Foundational papers on machine learning of intraoperative data have reported inconsistent results. Prasad et al. analyzed data from 101 patients undergoing liver transplantation and showed that intraoperative hemodynamic data improved the prediction of mortality and acute renal failure compared to preoperative information alone (22). On the contrary, Lee et al. found that a deep neural network model predicted in-hospital mortality, though not better than conventional models such as the Risk Stratification Index (23). It is important for clinicians to understand the factors and processes by which the machine learning algorithm built the model, to help with clinical decision making and hypothesis generation for future research. Thus, we have chosen machine learning techniques that generate interpretable models. Our use of a large population database and advanced machine learning methods may help improve our understanding of the crucial relationships amongst hemodynamic variables and complex perioperative data.

The results of this study may help synthesize complex intraoperative clinical information and unveil novel therapeutic strategies. Derived from data from the QEII Hospitals, the results would be directly applicable to the care of Nova Scotians. The models may lead to the creation of objective risk stratification scores calculated at the end of surgery, to identify high risk patients for increased postoperative follow-up and monitoring. Moreover, if models created using machine learning perform well, machine learning may be used more frequently to reveal the patterns within complex, large perioperative datasets. Hemodynamics are potentially modifiable risk factors. Future research includes prospective studies on whether targeted hemodynamic goals, increased postoperative follow-up of high-risk patients, and real-time machine learning precision medicine could improve outcomes after surgeries.

Specific aims

1. To use machine learning techniques to investigate systematically intraoperative hemodynamic predictors of postoperative 30-day all-cause mortality (primary outcome) and major in-hospital morbidity. Hemodynamic predictors to be studied are blood pressure, heart rate, oxygen saturation, end-tidal carbon dioxide, and medications to adjust blood pressure. Please see "Outcomes" section below for full list of secondary outcomes.
2. To evaluate performance of machine learning models created and compare the performance of the best model to the Surgical Apgar Score.

Hypothesis

Controlling for other predictors, the durations of mean arterial pressure (MAP) <65mmHg, heart rate <60 or >100 beats per minute (BPM), hemodynamic medications use, oxygen saturation (SpO_2) <88%, and end-tidal carbon dioxide ($EtCO_2$) <30 or >45 will be associated with postoperative 30-day all-cause mortality (primary hypothesis) and 30-day major in-hospital morbidity (secondary hypothesis). Note that blood pressure, heart rate, vasopressors and

inotropic medications, oxygen saturation, and end-tidal are considered key indicators of hemodynamics. We have chosen conventional ranges commonly used in practice, and will perform sensitivity analysis of different definitions of each hemodynamic variable.

In addition, the model for hemodynamic predictors of postoperative mortality developed from machine learning will perform better in terms of discrimination (C-statistics), calibration (Hosmer-Lemeshow test), and risk reclassification (Yates slope and integrated discrimination improvement) than the Surgical Apgar Score.

Methodology

Study Design Overview

This is a retrospective population cohort study. Following approval from the Research Ethics Board, we will analyze de-identified records of our study population. Since there are many machine modelling techniques each with its benefits and drawbacks, we will create models using interpretable machine learning techniques we believe will work the best for this study, and test the performances of these models through internal validation. The models will be compared to the Surgical Apgar Score in terms of discrimination, calibration, and risk reclassification. The trial will be registered on ClinicalTrials.gov prior to receiving research data and performing analysis. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) and Developing and Reporting Machine Learning Predictive Models (24) guidelines will be followed.

Study Population

We will include all patients ages ≥ 45 receiving their index (i.e. first) non-cardiac surgery with an overnight stay at the Nova Scotia Health Authority Queen Elizabeth II (QEII) hospitals (Victoria General and Halifax Infirmary) Halifax, Canada, from the past five years (i.e. January 1, 2013 to December 1, 2017). For patients who had multiple surgeries, only the first non-cardiac surgery with an overnight stay at QEII will be included to avoid confounding from previous surgical admissions (i.e. one surgical admission per patient). We chose December 1, 2017, as the end date to allow for complete data 30 days after surgery: for data analysis in summer 2019, we only have access to mortality data up to December 31, 2017

We will exclude patients with no intraoperative anesthetic records. Cardiac surgery patients (identified by procedure anatomy "Heart" or "Cardiac" within Innovian) are excluded since they have a unique set of considerations and complications due to having surgery directly in the heart. To include the full spectrum of non-cardiac surgical patients, no specific surgeries will be excluded except for deceased organ donation **(**"organ retrieval" in Innovian procedure name, and American Society of Anesthesiologists classification for neurologically-deceased organ donors, ASA=VI).

Preliminary analysis of our intraoperative database estimates approximately 35,000 patients in this cohort. For patients with multiple procedures, the date of the first surgical procedure with an overnight stay will be used to identify the specific surgical admission of interest.

Data Sources

The de-identified dataset will consist of databases from Innovian, Horizon Surgical Manager (HSM), and Health Data Nova Scotia (HDNS). Innovian is the intraoperative anesthesia electronic information management system used at the QEII, containing automated recordings of intraoperative standard monitors, time-stamped anesthesiology entries of medications and interventions, and perioperative laboratory tests. HSM contains vital signs and administrative data at the anesthetic preoperative clinic, in the preoperative area prior to the surgery, and in the recovery room after surgery.

The specific HDNS databases to which access is being requested are the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) and Vital Statistics. DAD is a repository of clinical and administrative data from each hospitalization, including preoperative diagnoses, surgery performed, postoperative complications, and investigations.

DAD includes the 25 most relevant diagnoses preoperatively and postoperatively. Nova Scotia physician billings data will not provide any additional relevant information and are not necessary for this project. The Vital Statistics database records all deaths within Nova Scotia. Innovian and HSM data will be linked together by health card number and surgical date by the Innovian Data Manager (Innovian-HSM dataset). The health card numbers will be sent to Medavie for encryption. HDNS will link the Innovian-HSM dataset with the HDNS variables by encrypted study IDs and surgery date. National and provincial privacy and data security policies will be strictly followed.

Data linkage:

Step 1: Innovian

a. Include patients with surgery dates 2013 Jan 1 – 2017 Dec 1 inclusive
b. Include patients with age on date of surgery ≥ 45
c. Exclude patients with procedure name that includes "organ retrieval" or ASA = VI, as well as procedure anatomy "heart" or "cardiac".
d. Eligible patients will be linked to HSM by health card number for the required variables described in the Appendix.

Step 2: HDNS: CIHI DAD

a. Health card numbers of patients identified in Step 1 will be sent to Medavie for encryption. Medavie will provide HDNS with encrypted health card numbers. HDNS obtains Study ID and Surgery date from the Innovian-HSM dataset to perform linkage via Study ID, encrypted health card number and procedure date (to ensure the data is from the same surgical admission). The maximum allowable mismatch for the surgery dates in Innovian and CIHI is +/- 1 day. The Innovian surgery date will be used as the gold standard, since the record is done in real time and thus the most accurate.
b. Exclude patients with Length of Stay (LOS) ≤ 1. If a patient had multiple surgeries, the first surgery with a LOS >1 (i.e. at least overnight stay) will be included.
c. HDNS provides Innovian-HSM the final list of included patients (patient ID and surgery date). Innovian-HSM will then send data for relevant variables to HDNS for linkage.

Data quality: Data reabstraction studies performed by the CIHI show high data quality, ranging from 76 to 96% for coding consistency of interventions reported, significant diagnoses, and most responsible diagnosis (25). Since intraoperative hemodynamic variables and laboratory are automatically recorded into Innovian, no validation is necessary. It would not be possible to retrospectively validate the anesthesiology physician entries into Innovian (e.g. use of vasopressor medications) as most are not recorded elsewhere, but with medical-legal requirements and more than 10 years of experience with Innovian at QEII, the error rates will likely not significantly affect results.

Variables

Please see Appendix for a detailed table of all variables.

I. Main Predictors ("Exposures")

At the time of surgery, anesthesiologists document the timing of key clinic information (induction, intubation, start and end of surgery, emergence, extubation, and exit of the operating room), medications and fluids administered, estimated blood loss, and type of anesthesia into the intraoperative record. Hemodynamic factors are automatically recorded into the database every minute. The following intraoperative hemodynamic factors will be included in model building:

Table 1. Exposures

Blood pressure	Since there is no universal definition of low blood pressure under anesthesia, we will use several different variables to determine the most significant exposure by threshold and duration. Both Systolic Blood Pressure (SBP) and Mean arterial pressure (MAP) have been used in blood pressure research (12). In a recent study (26), different blood pressure modeling techniques on the same dataset led to different conclusions on the impact of hypotension on postoperative myocardial infarction and kidney injury. Methods with the largest odds ratios were absolute maximum decrease in MAP and mean episode area under threshold. However, since the area under threshold is less interpretable and difficult to calculate in everyday clinical practice, the duration under threshold will be used. SBP 1. Maximum change from preoperative SBP, in a) absolute change (mmHg), and b) relative change (%)(emergency and elective cases analyzed separately due to the lack of preoperative blood pressure in the emergency group) 2. Cumulative duration (minutes) ≥20% below preoperative SBP 3. Longest single episode (minutes) below a) 80, b) 90, and c)100 mmHg 4. Cumulative duration (minutes) below a) 80, b) 90, and c)100 mmHg MAP 1. Maximum change from preoperative MAP, in a) absolute change (mmHg), and b) relative change (%) (emergency and elective cases analyzed separately due to the lack of preoperative blood pressure in the emergency group. Note that since the HSM database only contains SBP and DBP, not MAP, MAP will be calculated using MAP = 1/3*SBP + 2/3*DBP) 2. Cumulative duration (minutes) ≥20% below preoperative MAP 3. Longest single episode (minutes) below a) 60, b) 65, c) 70, and d) 80mmHg 4. Cumulative duration (minutes) below a) 60, b) 65, c) 70, and d) 80mmHg

Heart rate	Since both fast and slow heart rate may be harmful and there is no universal definition of abnormal heart rate under anesthesia, we will model using a variety of methods. 1. Maximum change (BPM) from preoperative heart rate (positive and negative) 2. Relative change (%) from preoperative heart rate (positive and negative) 3. Maximum pulse variation (maximum heart rate minus minimum heart rate) 4. Longest single episode (minutes) a) below 60, and b) above 100BPM 5. Cumulative duration (minutes) a) below 60, and b) above 100BPM
Use of hemodynamic medications (i.e. special medications for blood pressure)	1. Vasopressor/inotrope use (yes vs. no): phenylephrine, norepinephrine, epinephrine, vasopressin, dobutamine, or milrinone 2. Infusion of any vasopressor/inotropes above (yes vs. no) (identified by unit of weight over time) 3. Phenylephrine/ephedrine bolus (yes vs. no) (identified by unit of weight only) 4. Vasodilator use (yes vs. no): labetalol, esmolol, nitroglycerin, nitroprusside 5. Infusion of any vasodilator above (yes vs. no) (identified by unit of weight over time)
Oxygen saturation by pulse oximetry: SpO_2	1. Longest single episode (minutes) below a) 88, and b) 90% 2. Cumulative duration (minutes) below a) 88, and b) 90%
End-tidal (i.e. exhaled) Carbon dioxide: $EtCO_2$	1. Longest single episode (minutes) a) below 30, and b) above 45mmHg 2. Cumulative duration (minutes) a) below 30, and b) above 45mmHg

II. Outcomes

Primary: 30-day all-cause postoperative mortality (binary)

Secondary:

1. Major 30-day in-hospital morbidity, both in terms of the individual category (yes/no), and an overall composite (i.e. yes for any of the 6 categories vs. no). We have included major morbidity outcomes where increased monitoring would be beneficial, using International Statistical Classification of Diseases (ICD) 10 codes and based on published protocol on patient safety indicators (27).
    1. Cardiac: composite of acute myocardial infarction, cardiac arrest, ventricular tachycardia, congestive heart failure, pulmonary edema, complete heart block, shock excluding septic shock
    2. Respiratory: composite of pneumonia, pulmonary embolism, acute respiratory failure, respiratory arrest, Mechanical Ventilation ≥ 96 hours
    3. Acute Kidney Injury
    4. Cerebrovascular: composite of strokes and transient ischemic attacks
    5. Delirium
    6. Septic Shock
2. Postoperative ICU admission (yes/no)
3. Prolonged Postoperative Length of Stay (LOS) (greater than vs. less than or equal to CIHI Expected Length of Stay (ELOS) as assigned by the Case Mix Grouping) [note that the LOS includes the day of surgery]
4. Hospital readmission within 30 days (yes/no)
5. Intraoperative mortality (yes/no)
6. Days alive and out of hospital at 30 days postoperatively (28)

III. Other predictors included into model

The following potential perioperative predictors will be evaluated as covariates during model building. Statistically significant predictors will be retained in the model.

Table 2. Other predictors

Preoperative	1. Demographics: age on date of surgery, sex, obesity (body mass index>30) 2. Indicators of preoperative comorbidities: since no comorbidity score has perfect performance, a variety of models will be evaluated and the most significant predictive score will be retained in the model. • American Society of Anesthesiologist class • RCRI score(29), and specific components via ICD codes (history of ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes, chronic kidney disease, and CCI and Case Mix Group codes of suprainguinal vascular, intraperitoneal, or intrathoracic surgery) using previously published methods (30)(31) • Elixhauser comorbidity index (32) and Charleson Comorbidity Index (33): calculated using diagnoses from the previous three years according to standard algorithm by HDNS. Reported as both total score and individual categories • Hospital Frailty Risk Score (34): based on ICD codes • Preoperative blood pressure: ICD diagnosis of hypertension and by measured blood pressure • Preoperative heart rate: Innovian and HSM • Chronic Obstructive Lung Disease (ICD code): since it may affect the interpretation of results of SpO_2 and $EtCO_2$ 3. Indicators of surgical complexity • CIHI DAD Case Mix Group (CMG) class (also contains categories that include medical complexity) • Main Surgical Service • Procedural Index for Mortality Risk (PIMR) (35): according to CCI • Procedure: CCI codes • Preoperative ICU admission • Emergency surgery: as determined by DAD Method of Entry = emergency department or transferred from another institution)
Intraoperative	• Anesthetic factors o Type of anesthesia: General vs. regional vs. neuraxial vs. sedation (multiple concurrent types possible) o Measures of anesthetic depth ▪ Age-adjusted inspired Minimal Alveolar Concentration (MAC) – summed from all volatile anesthetics used (36). Since MAC is available for every 15 seconds, the average MAC for each case (i.e. time-weighted) will be used.

	▪ Bi-spectral Index (BIS): duration in minutes for BIS <46 (37) o Temperature: duration (minutes) a) < 36°C, and b) > 38°C (38) o Crystalloid administration >1L: volume in mL • Surgical factors o Duration o Laparoscopy o Bleeding: Estimated blood loss (mL), lowest Hemoglobin day within 2 days after surgery (g/L) (including day of surgery), Red Blood Cell transfusion (mL)

Analysis plan
Statistics will be analyzed directly on the HDNS Citadel secure server using SAS Software 9.4 (SAS Institute, Inc., NC) and R version 3.5.3 (https://www.r-project.org/).

Cohort characteristics
Descriptive statistics will be performed on all proposed predictors and outcome variables listed above. Continuous variables will be listed as mean with standard deviation, and categorical variables as frequency counts and percentages. Mortality will also be described in terms of causes, location (in- vs. out-of-hospital), and timing (intraoperative vs. postoperative, and by postoperative day).

Data processing and artifact removal
New variables will be created through calculation or dichotomization, as described in the variables section above and Appendix 1. Patients with age >120 or ≤ 45 will be flagged for further investigation of data validity and potential removal. Artifact removal from hemodynamic variables will be performed by the Innovian Database Manager in SQL, prior to creation of exposure variables (Table 1) and data linkage. Input of hemodynamic variables of interest (blood pressure, heart rate, $EtCO_2$, and SpO_2) as well as BIS and end tidal volatile from intraoperative monitors were automatically recorded every 15 seconds into Innovian. Continuous values were captured every 15 seconds as medians of 8 values captured every 2 seconds, while discrete values (e.g. NIBP) were captured as is at the moment. The maximum incidence of artifact was found to be 0.1% for heart rate, 0.4% for SpO_2, 2.9% for noninvasive blood pressure, and 15% for invasive blood pressure in a previous study (39), and this is likely an overestimate due to the strict definition of artifacts. A systematic review and cohort study showed that while a variety of different artefact algorithms affected the defined incidence of intraoperative hypotension, it did not significantly affect the model between hypotension and outcome (40). Importantly, duration-based hypotension definitions were less affected by artefact filtering algorithms than depth thresholds (40).

To reduce artifacts outside of anesthesia time (e.g. arterial line is plugged in prior to patient arrival), the variables below will only be taken during a defined "Surgery Duration". This Duration starts at the first valid recorded SpO_2 (that is subsequently valid for 1 minute), and ends after the last valid SpO_2 (that has been valid for 1 minute).

- **Blood pressure**
    1. **Step 1, removal of individual artifacts**: Note that non-invasive (NIBP) and invasive blood pressure values (IABP) will be treated separately. Potential artifacts will be removed (changed to missing data) in the following order:
        1. Missing any of SBP, DBP, or MAP, or where any of SBP, DBP, and MAP are equal to each other
        2. Apply 3 different artifact algorithms simultaneously to identify artifacts:
            - Multi-Centre Perioperative Outcomes Group (MPOG) algorithm
            - For IABP only: MAP value greater than 50% from the values before and after will be deleted, as previously described by Sun et al (41).

- The following blood pressure artifact removal rules as described by Salmasi et al (41) will also be applied: "SBP less than or equal to DBP + 5 mmHg", and "abrupt changes defined by SBP change greater than or equal to 80 mmHg within 1 min in either direction or abrupt SBP changes greater than or equal to 40 mmHg within 2 min in both directions."

3. To remove artifacts prior to arterial line insertion, for IABP data only, the first MAP readings must be >40, and the first SBP reading must be >60.
4. For each BP measurement, if any of SBP or MAP has been labelled as an artifact, then remove the entire measurement
5. If an entire case has been identified as null after artifact removal (i.e. no valid BP for the entire case), the entire case and studyID will be deleted.

2. **Step 2. Concatenation.** The final blood pressure will be taken from IABP or NIBP, whichever is available after artifact removal. If both non-invasive (NIBP) and invasive blood pressure values (IABP) are available for the same 15 second interval, the higher reading will be taken. Otherwise, the only blood pressure that is valid will be used.
3. **Clarification re. "Baseline" blood pressure:** The HSM and first Innovian BP will be modeled separately during analysis, i.e. each patient will have two "baseline" measurements, coded by the variables "MAP_first_Innovian" and "MAP_preop_HSM".
    1. All patients will have the variable of a first Innovian BP (after artifact clean up). The first Innovian BP is used since the second BP may be postinduction. This has the limitation that the the first intraoperative BP may not reflect the true baseline (42); however, practically this would be the blood pressure that would be available in similar clinical situations.
    2. Only some patients will have HSM BP (i.e. at preoperative clinic or in the preadmission area). Since the HSM does not contain MAP, MAP will be calculated using MAP = (2/3 DBP) + (1/3 SBP).
        - If a patient does not have a HSM BP, the variable value will be coded as missing (not zero).

- **Heart rate**

1. Artifact removal:
    1. The heart rate will be collected from the pulse oximeter instead of ECG, to reduce risk of electric cautery artifact and non-transmitted conduction.
    2. Heart rate > 170 or < 30 BPM will be removed. To reduce the influence from outlier artifacts (e.g. temporary disconnection or adjustment of a monitor), single episodes of deviation in any variable greater than 50% above or below the preceding value will be flagged. If the flagged heart rate from the pulse oximeter and ECG (and/or arterial line) differ by >10, the heart rate will be removed as artifact.
2. Clarification about "Baseline" heart rate: similar to BP above, the HSM and first Innovian HR will be modeled separately during analysis, i.e. each patient will have two "baseline" HR. All patients will have the variable of a first Innovian HR (after artifact clean up). Only some patients will have HSM HR (i.e. preoperative clinic or in the preadmission area). If a patient does not have a HSM HR, the variable value will be coded as missing (not zero).

- **$EtCO_2$** will only be analyzed in cases involving general anesthesia. Values > 120 or < 5 mmHg will be removed as artifact.
- **SpO_2** > 100% or < 50% will be removed as artifact.
- **Temperature** < 30 or > 43 degrees Celsius will be removed as artifact.
- **End tidal volatile concentrations** (including nitrous oxide) will be converted to summed age-adjusted MAC (36). The total age-adjusted MAC < 0.2 and >2.5, at each 15 second interval, will be removed as artifact prior to calculation of the time-weighted average (15 second time intervals).

For each automatically recorded variable from Innovian, at least 3 cases will be reviewed to ensure correct artifact labeling. We will quantify the percentages of artifacts flagged and removed per case for each variable monitored.

Artifact Removal Sub-study: Derivation of a machine learning algorithm for artifact removal for invasive blood pressure data

Rationale

While putting together the Innovian dataset for our study, we found that existing artifact (noise) removal algorithm has limitations at removing invasive arterial blood pressure (IABP) artifacts. Current algorithms are based on clinician-generated rules (40). We plan to use machine learning algorithms to improve artifact detection.

Objective

Our goal is to derive an artifact removal algorithm for IABP using machine learning of hemodynamic data.

Methodology

For this sub-study, we will include patients with IABP recorded. There are approximately 6000 patients with IABP recordings. We will exclude patients who do not have any recording of the required hemodynamic variables: IABP systolic, IABP mean, IABP diastolic, non-invasive blood pressure (NIBP) systolic, NIBP mean, NIBP diastolic, IABP heart rate, ECG heart rate, SpO2 heart rate, and SpO2 (oxygen saturation).

To label the dataset with "gold-standard" answers, we will use a random sample of 60 cases (chosen by random number generator) for which the artifacts (anomalies) will be manually labeled by anesthesiologists on the study team, blinded to the final artifact removal algorithm.

The problem of artifact detection (anomaly detection) will be addressed for two target variables: IABP mean and IABP systolic. We will use the same methodology to conduct the analysis for artifacts detection in these two target variables.

For each target variable the problem will be tackled in two approaches: as a univariate time series and as a multivariate time series. In the univariate series approach, we will only take into consideration the data of the time series representing either the IABP mean or the IABP systolic artifacts. For the multivariate approach, we will include the information of the following variables IABP systolic, IABP mean, IABP diastolic, NIBP systolic, NIBP mean, NIBP diastolic, IABP heart rate, ECG heart rate, SpO2 heart rate, and SpO2 (oxygen saturation).

In the univariate case, the anomaly detection will be carried out using several statistical approaches, and machine learning approaches.

Methods to apply for anomaly detection in the univariate time series case:

1) Statistical-based approaches: ARIMA model, simple, double and triple Exponential Smoothing and Outlier Detection using Prediction Confidence Interval (PCI). Anomalies will be detected by evaluating the deviation of the predicted point to the observed one.

2) ML-based approaches: DBSCAN, LOF, isolation Forest, One-Class Support Vector Machine, XGBoost and neural networks.

Regarding the anomaly detection in the multivariate time series case we will apply several machine learning-based techniques such as isolation forest, One-Class Support Vector Machine, XGBoost and different neural networks.

Regarding the performance evaluation, we will split the data set into train/test (70%) and validation (30%). This means we will use 42 cases for train and test and 18 cases for validation. The performance evaluation in the train/test part of the data will be carried out using 100 repetitions of bootstrapping method and we will assess the performance on following metrics: F_1, precision, recall, specificity, Negative Predicted Value (NPV), False Discovery Rate (FDR), G-Mean, AUC-ROC, AUC-PR.

The derived algorithm will be applied to the full sample (~6000 excluding the 60 cases used above), and the percentage of hypotension defined will be quantified according to published comparisons (1). This will also be compared to the results of the MPOG algorithm.

Analysis will be performed in Python.

Research Ethics Considerations

This sub-study will use the existing Innovian dataset, but using only the following completely de-identified variables:

1. Study ID
2. Time stamps for each hemodynamic variable (dates will be removed, and placeholders will be used to denote surgery times that happened overnight that bridges two dates)
3. Required timestamped hemodynamic variables for modelling:
IABP systolic

IABP mean
IABP diastolic
NIBP systolic
NIBP mean
NIBP diastolic
IABP heart rate
ECG heart rate
SpO2 heart rate
SpO2 (oxygen saturation)

Data analysis will be performed by Dr. Paula Branco (member of the current study team as a post-doc, currently faculty member at University of Ottawa) and her Co-op student Mengqi Wu will receive the de-identified, limited Innovian dataset securely and directly from our Innovian manager using the NSHA encrypted institutional email (SENDNS). The files will be stored in a password-protected computer and permanently deleted according to NSHA policy once analysis is complete (estimated to be end of September 2020).

Missing data

Since intraoperative hemodynamics are automatically recorded and mortality reporting is mandatory, we do not expect significant missing data for the key hemodynamic predictors and primary outcomes. For disease conditions, patients without ICD codes are assumed to not have the disease; the same applies for medications. For the other variables of interest, if there is less than 5% missing data, no processing will be performed. Between 5-20%, missing data will be imputed using group mean (43) for continuous variables. At greater than 20% missing data, the variable will be removed from analysis with potential causes evaluated and reported.

Creating the models

We will divide the cohort temporally (approximately 80:20 ratio) into two groups: derivation/training group (approx. January 1, 2013 – Dec 31, 2016), and validation group (approx. Jan 1, 2017 – December 1, 2017). This temporal approach to the model building vs. validation groups will also mirror the real-life application of machine learning, where data from the past is used to predict future outcomes. Splines will be used for the hemodynamic predictors involving time as a unit.

In the derivation/training set, we will create models for the *primary outcome* using machine learning techniques, including logistic regression with variable selection, classification trees, and Principal Component Analysis (PCA)(21). We have chosen these techniques to obtain interpretable results, i.e. being able to understand the process by which the algorithm decision making occurred. Also, these techniques demonstrate different approaches and perspectives to better understand the relationships amongst the variables.

Logistic regression with variable selection (e.g. LASSO, Elastic Net) identifies the most important predictors to create a parsimonious model. Classification trees predict outcomes based on input variables through classification. Random forest is an ensemble method of classification trees; while it is not directly interpretable, it can show which predictor has the highest importance. Association rule learning will be used to find new patterns. PCA is used for

dimensionality reduction and is particularly helpful in this study to better understand profiles of correlated variables, and to narrow down on what the most important predictors are when a multitude of predictors exist. PCA reveals components (i.e. groups of correlated predictors), with the most important components accounting for the most variation within the data. Components found to account for the most variances (Eigenvalue ≥1) in a scree plot represent the most important sets of predictors. They will be further analyzed using Cronbach Alpha to assess for internal consistency within components. Note that since PCA is a method of unsupervised learning where the outcome is not defined, in the first PCA model, all variables (including both primary and secondary outcomes) will be inputted into PCA with the significant components reported. This is to generate profiles of correlated predictors and outcomes. Structural equation modeling will be used. In an unrelated, second PCA model, PCA will be used to reduce dimensionality of predictor variables (i.e. exposures and covariates only), and the most correlated predictors within key components will be entered into a logistic regression the primary outcome.

Class Imbalance

Since patients with the primary outcome of mortality only accounts for an estimated 1.7% of the sample, significant class imbalance exists (i.e. not a 1:1 ratio between patients with vs. without mortality). This results in the machine learning to be more focused on the majority class (i.e. patients without mortality) and impacts the predictive power for mortality.

Several techniques exist to make the learning algorithms to focus on the important class (44). Among these, pre-processing techniques are a powerful tool enabling the use of any standard learning algorithm by modifying the training set. The goal is to obtain a more balanced training set through weighting, undersampling and/or oversampling. We will explore different resampling techniques to rebalance the training set. Regarding undersampling, we will explore both random and informed undersampling (remove examples near the decision border through nearest neighbours computation and use a clustering algorithm to guide the selection of examples). For oversampling, we will explore the introduction of replicas (randomly or by weighting) and the generation of synthetic data through the introduction of Gaussian Noise, SMOTE, and other SMOTE-based techniques. We will also examine the combination of these techniques. All of these techniques are only applied on the training set used to learn the model, and they are never applied on the test set. Thus, the model, although learned in a more balanced scenario is always evaluated only in real data and in a real imbalanced scenario.

We will also apply cost-sensitive learning. The assignment of higher costs to type II errors during learning has the potential to improve the results, reducing this type of error. The effect of class rebalancing (at a variety of ratios and trough a variety of techniques) on model performance will be examined, and the impact of these adjustments on model performance will be reported.

Evaluating model performance

Using the derivation/testing set, the performances of machine learning models generated will be evaluated by cross validation. To account for potential temporal effects and concept drift, Monte Carlo and prequential evaluation will be used (45). In addition, each model will be evaluated in terms of discrimination, calibration, and risk reclassification (21,46). Discrimination will be calculated through C-statistics using area under curve (AUC) of receiver operating characteristic curve (ROC). Calibration will be represented graphically using observed vs.

expected event rates in risk estimate deciles, and by the Hosmer-Lemeshow statistic. Brier score will be computed for discrimination and calibration. Risk reclassification will be quantified through Yates slope and integrated discrimination improvement. R-squared will be reported.

The performance of all models created will be evaluated in the validation set as part of internal validation using the same metrics of discrimination, calibration, and risk reclassification, and compared to the Surgical Apgar Score. Since there will likely be significant class imbalance and ROC curves may overestimate model performance, for each model, precision and recall curves (PRC), F score, average precision, and AUC will also be reported and compared. The best performing model will also be used to analyze for predictors for secondary outcomes. Sensitivity (recall, true positive rate), specificity, positive predictive value (precision), G-mean, negative predictive values, False Discovery Rates (FDR), optimism, and measures of association of hemodynamic thresholds for primary and secondary outcomes will be computed. Bayesian network causal inference analysis may be performed, to help increase interpretability.

Sensitivity and subgroup analysis

Sensitivity analysis will be performed for different definitions of hemodynamic derangements. Subgroup analysis will be performed based on age, sex, high preoperative risk (most significant indicator of preoperative comorbidity in Table 2, based on final model), RCRI, frailty (HFRS), preoperative hypertension, a select list of intermediate-high risk, gender-neutral elective surgery (please see Appendix – RCRI Protocol Table 1), emergency surgery, and type of anesthesia.

Power calculation

The 2016-2017 in-hospital mortality after major surgery in Nova Scotia is 1.7% (47). Using the Events Per Variable criterion (EPV) of at least 10 outcomes per predictor in the sample, the 1.7% mortality (408) out of an estimated sample size of 24,000 for the derivation/training group means that our model would be valid for up to 41 predictors for the primary outcome. However, the EPV may over or underestimate the limitations of the EPV criterion (48), square root of the mean squared prediction error (rMPSE) and mean absolute prediction error (MAPE) will be calculated based on the number of predictors, sample size and events fraction (49) with the caveat that this model has not been externally validated . Full power calculation will be performed once we receive the final sample size.

Strengths

This study involves a large, recent population dataset with nearly complete follow up for the primary outcome. There has been more than 10 years of experience with intraoperative anesthetic electronic recording system, with a high likelihood of provider proficiency with anesthetic intraoperative electronic documentation. This dataset is unique in North America for its degree of intraoperative details, pairing of clinical and administrative data, and robust data quality. Our use of machine learning could detect new network relationships and strategies that may inform current practice as well as future research.

Limitations

This study involves two academic provincial adult non-obstetric tertiary care centres in one hospital system, which may represent a sicker population. Validation in other centres would

increase generalizability. The retrospective nature of this database study makes it susceptible to random error, bias, and confounding. There may be cluster effects from health providers and hospitals, however the large sample size allows for robust power and minimizes random error. There is a potential for misclassification, measurement, and ascertainment bias. Due to the lack of universal screening for morbidity (e.g. troponin biomarker for myocardial injury and infarction, and Brain-Natriuretic Peptide for preoperative cardiac risk stratification), only mortality will be included as primary outcome. The lack of postoperative hemodynamic data creates non-informative censoring (i.e. unbiased since the data is missing for all patients). Numerous other predictors have been adjusted for through multivariate logistic regression but unknown confounders and confounding by indication may remain. The retrospective data reflects a snapshot of evolving practice, though secular effects may remain limited over the five-year study period. Future prospective validation of the prediction model will increase external validity.

Future directions

Future research includes prospective multicentre validation of our findings. Based on this model, a real-time risk prediction tool could be incorporated into electronic anesthesia management systems, while a simple score could be developed for clinicians. In addition, randomized studies could shed light on whether targeted hemodynamics, increased postoperative follow-up based on risk stratification, and real-time machine learning precision medicine could improve mortality, morbidity, and patient-reported outcomes after surgeries.

Feasibility

Budget overview

Budget Item	Amount	Details
A. Personnel/third party service providers	$800	Mentorship from data analyst Lynn Lethbridge.
B. Equipment	$0	SAS and R software will be provided by HDNS.
C. Materials, supplies and administrative services	$5895 $75	Health Data Nova Scotia data request and linkage with Innovian and HSM. Medavie patient ID encryption (required by HDNS)
D. Knowledge translation and dissemination	$1600	Poster presentation at a conference
Total	**$8370**	

Additional budget details

Budget Item A: Lynn Lethbridge is a data analyst within the Department of Surgery with extensive experience with HDNS. She has been contracted to mentor Dr Ke's data analysis for 16 hours at $50/hour ($800).

Budget Item C: We will request Discharge Abstracts Database and Vital Statistics data from Health Data Nova Scotia (HDNS) (please see confirmation of feasibility and quote attached). HDNS will link this dataset with our institutional Innovian (intraoperative anesthesia electronic record) by MSI and provide us with a complete de-identified dataset. No server purchase is necessary since the HDNS data will be provided on Citadel. Details from HDNS regarding Citadel: "Analyses will be carried out remotely on the HDNS Windows server "Citadel". Connection to Citadel occurs through Remote Desktop Connection (RDC). Citadel only accepts connections from approved DAL NetIDs to access specific project data housed in our Hadoop based research cluster. Other external connections such as the internet or USB devices are disabled, and no data may be transferred between the local PC and the remote session."

Budget Item D: Presentation at a conference: Poster printing $200, flights and accommodation $1000, registration fee $400.

Funding: $5000 Nova Scotia Health Authority Research Fund (awarded), the rest to be covered by the Dalhousie Department of Anesthesia

Benefits

This interdisciplinary study brings together investigators from diverse disciplines and locations, with expertise from Dalhousie anesthesiology, epidemiology, and Big Data Institute, as well as Harvard and University of Toronto. The research project is locally-based and relevant, with findings that may spark further research and inform anesthesiology perioperative practice.

The QEII hospitals are tertiary referral centres taking care of some of the sickest patients of the province. Better understanding of intraoperative predictors may unveil strategies to improve outcome and improve resource allocation after surgery. Moreover, this model may be generalizable to other hospitals, placing the Nova Scotia Health Authority and Dalhousie University as a leading innovator in this area, as large population-level outcomes research will likely continue to be at the forefront of health research.

Research team roles and responsibilities

Dr. Ke is completing the Harvard T.H. Chan School of Public Health Summer-Only Master of Science in Epidemiology. This consists of coursework over three summers (2018-2020) and online. The courses focus on epidemiology and advanced statistics, and with mentorship from Harvard and Dalhousie faculty Dr. Ke has been learning the theoretical knowledge and practical coding skills to independently analyze this project. She has protected research time to complete this project.

This proposed thesis project is co-supervised by Dalhousie and Harvard faculty. Dr. E. Francis Cook at the Harvard School of Public Health for his expertise in epidemiology, risk prediction, and data mining. Dr. George has extensive research experience in anesthesiology and has been building capacity in Big Data anesthesiology research at Dalhousie. Dr. David MacDonald at Dalhousie anesthesiology has expertise in perioperative medicine and will bring clinical and research knowledge. We also draw on the guidance of Dr. William Scott Beattie (anesthesiology professor at University of Toronto) who has published extensively in database studies involving perioperative outcomes, Dr. Robin Urquhart (Community Health & Epidemiology) for her experiences with Health Data Nova Scotia (HDNS) and epidemiology, Dr. Stan Matwin (Director at the Dalhousie Big Data Institute) for his expertise in machine learning and Big Data, Dr. Paula Branco (Post-doctoral fellow at Dalhousie Computer Science) for her specialty in machine learning and class imbalance, Dr. Luis Torgo (Professor at Dalhousie Computer Science) for his expertise in analytics of spacio-temporal data, Dr. Dan McIssac from Ottawa for his specialty in perioperative database research, George Campanis and Paul Brousseau for their experience with Innovian and medical informatics, and Lynn Lethbridge (Department of Surgery) for HDNS data analysis mentorship.

Knowledge translation and dissemination

The models derived from this project will undergo further prospective internal and external validation prior to being incorporated into clinical practice. Based on an externally validated model, a real-time risk prediction tool could be incorporated into electronic anesthesia management systems, while a simple score could be developed for clinicians. This project will be presented locally at the Dalhousie Anesthesia Research Day, as well as at a national or international anesthesiology conference. In addition, the methodology of optimization of class imbalance will be published in a machine learning journal, and the overall project will be published in an anesthesiology journal. Once published, a Visual Abstract and a patient-focused infographic of results will be disseminated on social media.

Ethical considerations

Use of Personal Health Information (PHI)

This is a minimal-risk study. De-identified patient data meeting the inclusion and exclusion criteria will be obtained from Innovian and Health Data Nova Scotia. This project satisfies all of the requirements for waiver of consent under the Tri-Council Policy Statement (TCPS 2) and Nova Scotia Personal Health Information Act (please see Request for Waiver of Consent appendix). The population size is estimated to be 35,000, which would be impracticable since this is an incredibly large population to contact for consent. Also, the cohort of interest includes patients aged 45 and older who have undergone surgery, and it is therefore expected that some patients would have died. Obtaining consent for these individuals would not only result in the re-identification of these patients, but also their next-of-kin who would give consent on their behalf. We have submitted a request for waiver of consent to the REB.

Measures will be in place to minimize the risk of breach in privacy and confidentiality (please see below). Due to the large sample size and the collection of common perioperative outcomes, accidental identification of a specific person from de-identified data is unlikely. There is no other adverse event, harm, or risk anticipated.

Health Data Nova Scotia will create a database of linked data using the Provincial Health Card number and date of surgery. The database we receive will be de-identified. PHI collected include the following and will be used in the most de-identified form:

1. Date of surgery (for patients with multiple surgeries, information from only the first surgery will be collected): in order to divide the cohort into derivation, training, and validation groups by date of surgery
2. Age on date of surgery, Sex: potential covariates in the model
3. Procedures (Current Procedural Terminology (CPT) codes: a potential covariate in the model

Measures Taken to Protect Personal Health Information and Study Data

- **Cohort creation:** The linked dataset will be created by HDNS through experienced personnel and established process, and follow Tri-Council guidelines. The dataset we receive for analysis will not contain any direct identifiers such as health card number and date of birth.
- **Controlled access:** Only authorized researchers in Nova Scotia will have access to de-identified person-level data. Aggregate data will be used as early as possible. While Dr. Ke is in Boston, if needed, Health Data Nova Scotia will perform data analysis on patient-level data using SAS protocol from team and send the rest of the team aggregate data for interpretation. The rest of the team will only have access to aggregate results after statistical analysis, with no identifiable information. All de-identified person-level electronic data will be securely stored in the HDNS secure server “Citadel”, where analysis will be performed without needing to download data from the secure server.

    - Details from HDNS regarding Citadel: "Analyses will be carried out remotely on the HDNS Windows server "Citadel". Connection to Citadel occurs through Remote Desktop Connection (RDC). Citadel only accepts connections from approved DAL NetIDs to access specific project data housed in our Hadoop based research cluster. Other external connections such as the internet or USB devices are disabled, and no data may be transferred between the local PC and the remote session."
- **Removal of all personal identifiers in electronic data:** This will be performed by the HDNS prior to the release of the analytic dataset to the project team.
- **The results of the study (prototypes, publications, posters, presentations) will not contain any personal data:** Only aggregate data of cell counts greater than 5 will be reported. As per HDNS policy, manuscripts will be submitted to HDNS for approval prior to publication to ensure privacy and confidentiality.

Storage and Retention of Personal Health Information and Study Data

De-identified electronic person-level data will be securely stored in Citadel, the HDNS server. (please see above). Paper material will be stored in a locked cabinet in the Halifax Infirmary Anesthesiology Research Office. Regulatory documents (no-PHI) will be stored in the secure (locked; access limited) anesthesia research office. Electronic records will be kept in password protected files on a password protected computer on the NSHealth network.

After study completion, according to HDNS protocol, researchers will no longer have access to Citadel but the data will be kept within HDNS for a minimum of seven years. Paper records will be securely shredded in accordance to NSHA policy. All electronic files will be permanently erased by the according to NSHA IT policy at the end of the retention period (7 years).

How do benefits outweigh harm

The results of this study may help synthesize complex intraoperative clinical information and unveil novel therapeutic strategies. Derived from data from the QEII Hospitals, the results would be directly applicable to the care of Nova Scotians. The QEII hospitals are tertiary referral centres taking care of some of the sickest patients of the province. Better understanding of intraoperative predictors may unveil strategies to improve outcome and improve resource allocation after surgery.

The models may lead to the creation of objective risk stratification scores calculated at the end of surgery, to identify high risk patients for increased postoperative follow-up and monitoring. Moreover, if models created using machine learning perform well, machine learning may be used more frequently to reveal the patterns within complex, large population perioperative datasets. Hemodynamics are potentially modifiable risk factors. Future research includes prospective studies on whether targeted hemodynamic goals, increased postoperative follow-up of high-risk patients, and real-time machine learning precision medicine could improve outcomes after surgeries.

With any database analysis project, a potential harm would be a breach in confidentiality and privacy. With robust measures detailed above to protect privacy and confidentiality strictly

followed, the risk of breaches is minimal. The many benefits of this study outweigh the unlikely occurrence of potential harms.

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Appendix 1. Summary of Variables

Source Dataset	Variable	Level of Identification	Time Span	Why is this element required in the analysis?
Information for inclusion and data linkage				
Innovian	**Date of surgery**	Patient	Jan 1, 2013 to Dec 1, 2017	Part of HDNS data linkage with Innovian to ensure only variables from the surgical admission of interest (first surgery admission with LOS>1) is included. This Date of Surgery will be used to confirm linkage with "PDATE" from CIHI DAD to ensure that data from the correct surgical admission is included The maximum allowable mismatch for the surgery dates in Innovian and CIHI is +/- 1 day. The Innovian surgery date will be used as the gold standard, since the record is done in real time and thus the most accurate. The date of surgery will also be used to divide the cohort temporally into the derivation/training group (January 1, 2013 – November 30, 2016), and validation group (December 1, 2016 – December 1, 2017)
Innovian	**Patient_ID**: encrypted health card number	Patient	Jan 1, 2013 to Dec 1, 2017	HDNS data linkage with Innovian. The dataset given to us will not contain Patient_ID, but rather a Study ID.
Innovian	**Age**: on date of surgery	Patient	Jan 1, 2013 to Dec 1, 2017	Age ≥45 part of inclusion criteria. Also, as age may impact outcomes, this will be included as a covariate in our models
Innovian	**Organ donation:** Procedure name	Patient	Jan 1, 2013 to Dec 1, 2017	Patients with procedure name that includes "organ donor" or "organ donation" will be excluded, since they are already declared brain dead and

	containing the word "Organ donor" or "Organ donation" or "DCD" [Derived by Innovian]			will not reflect the usual surgical population.
Innovian	**Cardiac surgery** [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	As defined by ProcedureAnatomy = "heart" or "cardiac". Cardiac surgery patients are excluded since they are receiving surgery directly on the heart and have a unique set of complications that may not reflect the usual surgical population.
Innovian	**ASA:** American Society of Anesthesiologist class (I to VI)	Patient	Jan 1, 2013 to Dec 1, 2017	Patients with ASA VI (i.e. patient with neurologic brain death for organ donation) will be excluded. Also, as this may affect outcomes, it will be included as a covariate in our models.
CIHI DAD	**PATIENT_ID**: encrypted health card number For HDNS internal use	Patient	Jan 1, 2013 to Dec 1, 2017	HDNS data linkage with Innovian-HSM. The dataset given to us will not contain Patient_ID, but rather a Study ID.
Vital Statistics	**PATIENT_ID**: encrypted health card number For HDNS internal use	Patient	Jan 1, 2013 to Dec 1, 2017	HDNS data linkage with Vital Statistics. The dataset given to us will not contain Patient_ID, but rather a Study ID.
CIHI DAD	**PDATE[1-n]**: procedure date	Patient	Jan 1, 2013 to Dec 1, 2017	HDNS data linkage with Innovian surgery date, to ensure that only the admission corresponding to the surgery admission of interest (first surgery admission with LOS>1) is included.

				The PDATE matching the date of procedure (+/- 1 day) from Innovian will be used. The corresponding number (e.g. PDATE1) will be used for all procedure-related codes (e.g. PCODE1, PDSERV1). Note that except for preoperative comorbidity data, where we would need data for 3 years prior to PDATE, for all other variables we only need data within 30 days after PDATE.
CIHI DAD	**LOS:** Length of Stay **(after surgery)** Derived by HDNS: discharge date minus PDATE + 1 (includes day of surgery)	Patient	Jan 1, 2013 to Dec 1, 2018 (to account for prolonged LOS postop from the end of inclusion date)	Part of inclusion criteria: if a patient had multiple surgeries, the first surgery with a LOS >1 (i.e. at least overnight stay). To calculate ratio of LOS to Expected Length of Stay (ELOS) as secondary outcome. We have chosen to standardize LOS to only include duration of stay after surgery, since there are many factors that may prolong a patient's stay prior to surgery.
Additional Demographic Information				
CIHI DAD	**SEX:** Patient sex	Patient	Jan 1, 2013 to Dec 1, 2017	As sex may affect outcomes, this will be included as a covariate in our models M = Male F = Female
HSM	**BMI:** Body Mass Index [Derived by Innovian]	Patient	Jan 1, 2010 to Dec 1, 2017	Dichotomized according to WHO definition for obesity: BMI>30. This will be combined with ICD code to create a binary Obesity variable (please see below).

CIHI DAD	**Obesity** [Derived by HDNS]	Patient	Jan 1, 2010 to Dec 1, 2017	Binary variable (yes/no), "yes" defined by: BMI >30, and if BMI missing, obesity ICD code (DXCODE[1-n] = E66). As BMI may affect outcomes, this will be included as a covariate in our models. The BMI data from HSM-Innovian will take precedent over DXCODE: i.e. first identify patients BMI>30 (coded as obesity = yes), BMI <=30, and BMI=missing data. For patients with BMI=missing, patients with ICD E66 will also be coded as obesity = yes.
Additional Measures of Perioperative Comorbidity				
CIHI DAD	**DXCODE [1-n]:** diagnosis code	Patient	Jan 1, 2010 to Dec 31, 2017 (3 years before and including 30 days after date of surgery)	Diagnosis codes are required for the following purposes: • HDNS will use DXCODE (with "*DXTYPE[1-n] = 1"*, **OR** "*DXTYPRE[1-n] = 2 AND DXPRE[1-n] = 5",* **OR** "*DXTYPE[1-n] = 3 AND DXPRE[1-n] = 5",* **OR** "*DXTYPE[1-n] = M AND DXPRE[1-n] = 5"*) within three years before date of surgery to calculate the Elixhauser comorbidity index, Charleson Comorbidity Index, RCRI, and Hospital Frailty Risk Score (see below). The entirety of DXCODES do not need to be disclosed to the research team since HDNS will perform the calculations. • Specific comorbid conditions will be included as covariates in the analysis • To examine post-operative comorbidity

				<u>Comorbidity covariates:</u> We need the following DXCODE (with "*DXTYPE[1-n] = 1"*, **OR** "*DXTYPRE[1-n] = 2 AND DXPRE[1-n] = 5",* **OR** "*DXTYPE[1-n] = 3 AND DXPRE[1-n] = 5",* **OR** "*DXTYPE[1-n] = M AND DXPRE[1-n] = 5"*) within 3 years <u>before PDATE</u>: Disease categories for RCRI (please see "RCRI"); hypertension (I10-I15), COPD (I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3), Obesity (E66) <u>Postoperative outcomes:</u> We need the following DXCODE (with "DXTYPE [1-n]=2" Excluding "DXTYPE [1-n]=2 AND DXPRE [1-n]=5", **OR** "DXTYPE [1-n]=3" excluding "DXTYPE [1-n]=3 AND DXPRE [1-n]=5", **OR** "*DXTYPE[1-n] = M AND DXPRE[1-n] = 6"*) to include into model as individual, categorical, and composite secondary outcome: **Cardiac:** acute myocardial infarction (I21 to I22, I24), cardiac arrest (I46.0, 146.1, I46.9), ventricular tachycardia (I47.2), shock (R57, T81.1) excluding septic shock (R57.2), congestive heart failure (I50.0, I50.1, I50.9), pulmonary edema (J81), complete heart block (I44.2) **Respiratory:** pneumonia (J13 to J18, J69.0, J69.8, J95.4), pulmonary embolism (I26), acute respiratory failure (J95.1, J95.2, J96.0), respiratory arrest (R9.2)

				Cerebrovascular: strokes and transient ischemic attacks (I60 to I69, G45) **Delirium** (F5) **Acute kidney injury (**N17) **Septic shock** (R57.2)
CIHI DAD	**DXPRE [1-n]:** diagnosis prefix	Patient	Jan 1, 2010 to Dec 31, 2017 (3 years before and including 30 days after date of surgery)	To categorize the type of the corresponding DXCODE (please see above): C = Cause of death Q = Query Diagnosis/Etiology 5 = Comorbidity arose before qualifying intervention 6 = Comorbidity arose during or after qualifying intervention 8 = Palliative Care
CIHI DAD	**DXTYPE [1-n]:** diagnosis type	Patient	Jan 1, 2010 to Dec 31, 2017 (3 years before and including 30 days after date of surgery)	To categorize the type of the corresponding DXCODE (please see above): M = Most Responsible Diagnosis 1 = Pre-admit comorbidity 2 = Post-admit comorbidity 3 = Secondary Diagnosis
CIHI-DAD	Admit-date	Patient	1Jan2010 to 31Dec2017	For 3-year look-back window with: either admission date or discharge date is between surgery date (B) and 3 years before B (A), assuming that A<B. For 30-day follow-up window with: Either admission date or discharge date is between surgery date (B) and 30 days after B (C), assuming that B<C.
CIHI-DAD	Discharge_date	Patient	1Jan2010 to 31Dec2017	For 3-year look-back window with: either admission date or discharge date is between surgery date (B) and 3 years before B (A), assuming that A<B.

				For 30-day follow-up window with: Either admission date or discharge date is between surgery date (B) and 30 days after B (C), assuming that B<C.
CIHI DAD	**ECI:** Elixhauser comorbidity index [Derived by HDNS]	Patient	Jan 1, 2010 to Dec 1, 2017 (3 years before and including date of surgery)	To be computed by the HDNS according to protocol (32) using DXCODES (please see above), to be included into model as covariate. Please report both total score, and any of the following individual categories: Congestive heart failure Cardiac arrhythmias Valvular disease Pulmonary circulation disorders Peripheral vascular disorders Hypertension, uncomplicated Hypertension, complicated Paralysis Other neurological disorders Chronic pulmonary disease Diabetes, uncomplicated Diabetes, complicated Hypothyroidism Renal failure Liver disease Peptic Ulcer Disease Excluding Bleeding AIDS/HIV Lymphoma Metastatic cancer Solid tumor without metastasis Rheumatoid arthritis/ collagen vascular diseases Coagulopathy Obesity Weight loss Fluid and electrolyte disorders Blood loss anemia Deficiency anemia Alcohol abuse Drug abuse Psychoses

				Depression
CIHI DAD	**CCI:** Charleson Comorbidity Index [Derived by HDNS]	Patient	Jan 1, 2010 to Dec 31, 2017 (3 years before and including 30 days after date of surgery)	To be computed by the HDNS according to protocol (33) using DXCODES (please see above), to be included into model as covariate. Please report both total score, and any of the following individual categories: Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Rheumatic disease Mild liver disease Moderate or severe liver disease Diabetes without chronic complication Diabetes with chronic complication Hemiplegia or paraplegia Renal disease Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin Metastatic solid tumor Peptic Ulcer Disease Excluding Bleeding AIDS/HIV
CIHI DAD	**RCRI:** Revised Cardiac Risk Index [Derived by HDNS]	Patient	Jan 1, 2010 to Dec 1, 2017 (3 years before and including date of surgery)	As RCRI has been shown to affect outcomes (29), it will be included as a covariate. This is based on DXCODE ICD codes (identified above) of history of ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes on insulin, chronic kidney disease creatinine >176.8 µmol/L, and a list of Canadian Classification of Health Interventions (CCI codes) of

				suprainguinal vascular, intraperitoneal, or intrathoracic surgery (30). Detailed protocol will be sent to the HDNS. Please provide both the names of the categories and the total score (i.e. for each patient, positive for any of the categories of cerebrovascular disease, ischemic heart disease, congestive heart failure, chronic kidney disease, diabetes, and diabetes on insulin; as well as the total RCRI score (1 point for each positive category).
CIHI DAD	High risk surgery as per RCRI: Suprainguinal vascular, intraperitoneal, or intrathoracic surgery [Flag - Derived by HDNS]	Patient	3 years before and including date of surgery (i.e. Jan 1, 2010 to Dec 1, 2017)	Binary variable (yes/no) As this may affect outcomes, it will be included as a covariate by itself and as part of the Revised Cardiac Risk Index (RCRI) score calculation.
HSM	Preoperative insulin use (yes/no) [Derived by Innovian: yes = any insulin use in the preoperative medication list]	Patient	3 years before and including date of surgery (i.e. Jan 1, 2010 to Dec 1, 2017)	Due to the difficulty of obtaining this data from ICD codes (the code for this, Z79.4, only came to existence in 2018), this will help identify patients on insulin for the RCRI score.
Innovian (from linked lab database)	Preoperative Creatinine (µmol/L)	Patient	3 years before and including date of surgery (i.e.	This will help identify patients who satisfy the chronic kidney disease category (Pre-operative creatinine >176.8 µmol/L) to calculate the RCRI score.

			Jan 1, 2010 to Dec 1, 2017)	
CIHI DAD	**HFRS:** Hospital Frailty Risk Score [Derived by HDNS]	Patient	3 years before and including date of surgery (i.e. Jan 1, 2010 to Dec 1, 2017)	As the HFRS has been shown to affect outcomes, it will be included as a covariate. HDNS will calculate using DXCODE according to a published protocol (34). Detailed protocol will be sent to the HDNS.
Innovian and HSM	Preoperative mean arterial pressure (MAP) [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	As preoperative high blood pressure may affect the interpretation of the threshold of harm for intraoperative blood pressure (12), preoperative MAP will be used in the calculation of change in MAP (absolute and %). HSM contains blood pressure of elective surgery patients at the anesthetic clinic and prior to entering the operating room, while Innovian contains the first blood pressure of all patients in the operative room. The lowest blood pressure from either Innovian or HSM will be used.
HSM	Preoperative systolic blood pressure (SBP) [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	As preoperative high blood pressure may affect the interpretation of the threshold of harm for intraoperative blood pressure (12), preoperative SBP will be used in the calculation of change in SBP (absolute and %). HSM contains blood pressure of elective surgery patients at the anesthetic clinic and prior to entering the operating room. The first Innovian blood pressure will be used for emergency surgery patients, since HSM pressure will not be available.

Innovian	First systolic blood pressure (SBP) [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Emergency and elective cases will be analyzed separately for the variables containing relative SBP changes, recognizing the lack of preoperative blood pressure in the emergency group. For patients with BP recorded on HSM (i.e. preoperative clinic or in the preadmission area), the lowest of the HSM or first Innovian BP will be used as baseline. For emergency surgery patients without previously recorded blood pressure, the first Innovian BP will be used (since the second BP may be postinduction), with the limitation that this may not reflect the true baseline (42); however, practically this would be the blood pressure that would be available in similar clinical situations.
HSM	Preoperative mean arterial pressure (MAP) [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Since the HSM database only contains SBP and DBP, not MAP, MAP will be calculated using MAP = 1/3*SBP + 2/3*DBP
Innovian	First mean arterial pressure (MAP) [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Emergency and elective cases will be analyzed separately for the variables containing relative MAP changes, recognizing the lack of preoperative blood pressure in the emergency group. For patients with BP recorded on HSM (i.e. preoperative clinic or in the preadmission area), the lowest of the HSM or first Innovian BP will be used as baseline. For emergency surgery patients without previously recorded blood pressure, the first Innovian BP will be used (since the second BP may be postinduction), with the limitation that this may not

				reflect the true baseline (42); however, practically this would be the blood pressure that would be available in similar clinical situations.
HSM	Preoperative heart rate	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect the level of harm from the intraoperative heart rate, it will be used in the calculation of change in heart rate (absolute and %) HSM contains heart rate of elective surgery patients at the anesthetic clinic and prior to entering the operating room, while Innovian contains the initial heart rate of all patients in the operative room. The lowest heart rate from either Innovian or HSM will be used.
Innovian	Preoperative heart rate	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect the level of harm from the intraoperative heart rate, it will be used in the calculation of change in heart rate (absolute and %) HSM contains heart rate of elective surgery patients at the anesthetic clinic and prior to entering the operating room, while Innovian contains the initial heart rate of all patients in the operative room. The lowest heart rate from either Innovian or HSM will be used.
CIHI DAD	Emergency surgery [Derived by HDNS] **ENTRYCOD**: method of entry	Patient	Jan 1, 2013 to Dec 1, 2017	ENTRYCOD = E (i.e. emergency department) and/or ADFROM = [any except 085 (QEII) – i.e. transferred from another institution] excluding elective admission (flag) will be used to identify surgeries as emergency surgery. As the emergency nature of surgery has been shown to affect outcomes, it will be included as a covariate.

	ADFROM: Institution from Number			
CIHI DAD	**ADTYPE:** Admission Type	Patient	Jan 1, 2013 to Dec 1, 2017	This variable will be used internally by HDNS to create a flag for elective admission. This will not be included in the dataset. This will help identify patients who did not have emergency surgery.
Indicator of surgical complexity				
CIHI DAD	**CMG**: Case Mix Group ("a grouping methodology developed by CIHI that categorizes acute care patients into groups based on similarities of diagnosis, intervention, LOS, and resource requirements. ")	Patient	Jan 1, 2013 to Dec 1, 2017	All CMG will be included into modeling to determine the CMG with the highest postoperative risk.
CIHI DAD	**PIMR:** Procedural Index for Mortality Risk [Derived by HDNS]	Patient	Jan 1, 2013 to Dec 1, 2017	As the PIMR has been shown to affect outcomes, it will be included as a covariate. HDNS will calculate using DXCODE according to a published protocol (35). Detailed protocol will be sent to the HDNS.
CIHI DAD	**Subgroup analysis flag: intermediate to high risk, gender neutral elective surgeries**	Patient	Jan 1, 2013 to Dec 1, 2017	To create a list of intermediate to high risk, gender neutral elective surgeries for subgroup analysis. Detailed list of CCI codes will be sent to the HDNS.

	[Derived by HDNS based on PCODE]			
CIHI DAD	**PCODE[1-n]:** Procedure [1-n] Code, according to Classification of Health Interventions (CCI). The one PCODE corresponding to the specific PDATE will be obtained, i.e. the corresponding number (e.g. PDATE1) will be used for all procedure-related codes (i.e. PCODE1)	Patient	Jan 1, 2013 to Dec 1, 2017	Covariate in model The PCODE corresponding to the included PDATE for each patient will be included for modeling as a covariate.
CIHI DAD	**PDSERV**[1-n]: Procedure [1-n] Doctor service The one PDSERV corresponding to the specific PDATE will	Patient	Jan 1, 2013 to Dec 1, 2017	The one PDSERV corresponding to the included PDATE allows us to determine the surgical service, and since the type of surgery may affect outcomes, it will be included as a covariate. We will include the following PDSERV: 00030 General Surgery 00031 Cardiac Surgery 00032 Neurosurgery 00034 Orthopedic Surgery 00035 Plastic Surgery

	be obtained, i.e. the correspondin g number (e.g. PDATE1) will be used for all procedure-related codes (e.g. PDSERV1)			00036 Thoracic Surgery 00037 Vascular Surgery 00039 Urology 00050 Obstetrics and Gynecology 00059 Colorectal Surgery 00060 Otolaryngology 00073 General Surgical Oncology
Intraoperative variables				
Innovian	**SBP:** Systolic blood pressure [Derived by Innovian as multiple variables – see right]	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: 5. Maximum change from preoperative SBP, in a) absolute change (mmHg), and b) relative change (%)(emergency and elective cases analyzed separately due to the lack of preoperative blood pressure in the emergency group) 6. Cumulative duration (minutes) ≥20% below preoperative SBP 7. Longest single episode (minutes) below a) 80, b) 90, and c)100 mmHg 8. Cumulative duration (minutes) below a) 80, b) 90, and c)100 mmHg
Innovian	**MAP:** Mean Arterial Pressure	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: 1. Maximum change from preoperative MAP, in a) absolute change (mmHg), and

	[Derived by Innovian as multiple variables – see right]			b) relative change (%) (emergency and elective cases analyzed separately due to the lack of preoperative blood pressure in the emergency group. Note that since the HSM database only contains SBP and DBP, not MAP, MAP will be calculated using MAP = 1/3*SBP + 2/3*DBP) 2. Cumulative duration (minutes) ≥20% below preoperative MAP 3. Longest single episode (minutes) below a) 60, b) 65, c) 70, and d) 80mmHg 4. Cumulative duration (minutes) below a) 60, b) 65, c) 70, and d) 80mmHg
Innovian	**HR:** Heart rate [Derived by Innovian as multiple variables – see right]	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. Emergency and elective cases analyzed separately due to the lack of preoperative heart rate in the emergency group. The following variables will be derived by Innovian: 6. Maximum change (BPM) from preoperative heart rate (positive and negative) 7. Relative change (%) from preoperative heart rate (positive and negative) 8. Maximum pulse variation (maximum heart rate minus minimum heart rate) 9. Longest single episode (minutes) a) below 60, and b) above 100BPM 10. Cumulative duration (minutes) a) below 60, and b) above 100BPM
Innovian	**Use of hemodynamic medications**	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: 6. Vasopressor/inotrope use (yes vs. no): phenylephrine,

	[Derived by Innovian as multiple variables – see right]			norepinephrine, epinephrine, vasopressin, dobutamine, or milrinone 7. Infusion of any vasopressor/inotropes above (yes vs. no) (identified by unit of weight over time) 8. Phenylephrine/ephedrine bolus (yes vs. no) (identified by unit of weight only) 9. Vasodilator use (yes vs. no): labetalol, esmolol, nitroglycerin, nitroprusside 10. Infusion of any vasodilator above (yes vs. no) (identified by unit of weight over time)
Innovian	**SpO_2 :** Oxygen saturation by pulse oximetry [Derived by Innovian as multiple variables – see right]	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: 3. Longest single episode (minutes) below a) 88, and b) 90% 4. Cumulative duration (minutes) below a) 88, and b) 90%
Innovian	**$EtCO_2$**: End-tidal (i.e. exhaled) [Derived by Innovian as multiple variables – see right]	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: 1. Longest single episode (minutes) a) <35, and b) >45 2. Cumulative duration (minutes) below a) <35, and b) >45
HSM	**Duration of surgery**	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect outcomes, it will be included as a covariate
Innovian	**Type of anesthesia**	Patient	Jan 1, 2013 to Dec 1, 2017	Categorical variable: general, neuraxial, peripheral nerve block, and/or managed anesthesia care [i.e.

				sedation] – multiple concurrent possible). As this may affect outcomes, it will be included as a covariate. Innovian will be used instead of the CIHI ANATYP (Anaesthetic Type), since anesthetic type is a mandatory field in Innovian and will allow for multiple concurrent anesthetic types.
Innovian	**Average MAC-adjusted:** Minimal Alveolar Concentration adjusted by age [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Age-adjusted MAC will be calculated by Innovian from the end-tidal % of all inspired volatiles according to published protocol (36). The MAC, available every 15 seconds will be averaged (i.e. time-averaged MAC). The averaged MAC will be included as a covariate.
Innovian	**BIS** : Bi-spectral Index [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Duration in minutes for BIS <46. As deep anesthesia (low BIS) may affect outcomes (50), it will be included as a covariate.
Innovian	**Laparoscopy-booked** [Derived by Innovian]	Patient	Jan 1, 2013 to Dec 1, 2017	Binary variable (yes/no), as defined by "laparoscope" or "laparoscopic" in procedure name.
DAD	**Laparoscopy converted to open flag STATUS[1-n]** **[Flag by HDNS]**	Patient	Jan 1, 2013 to Dec 1, 2017	Flag: STATUS[1-n] = C "Converted from endoscopic to open" Since Innovian procedure names are usually from OR booking, procedures where laparoscopy was converted to open would be included in the laparoscopy (booked) variable.

DAD	**Laparoscopy -actual [Derived by HDNS]**	Patient	Jan 1, 2013 to Dec 1, 2017	This is derived from as "laparoscopy-booked" excluding "laparoscopy converted to open flag" As this may affect outcomes, it will be included as a covariate.
Innovian	**Temperature [Derived by Innovian as multiple variables – see right]**	Patient	Jan 1, 2013 to Dec 1, 2017	Exposure variable to be included into modeling. The following variables will be derived by Innovian: duration (minutes) a) < 36°C, and b) > 38°C (38)
Innovian, HSM	**EBL: Estimated blood loss (mL)**	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect outcomes, it will be included as a covariate.
Innovian	**Crystalloid use >1000mL** **[Derived by Innovian]**	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect outcomes, it will be included as a covariate. Derived by Innovian as a continuous variable in mL, if Crystalloid >1000mL: Crystalloid = Ringer Lactate + Normal Saline + Plasmalyte + Normosol Note: this includes the total volume from infusions marked by mL/hour x hour infused
Innovian	**Hemoglobin: lowest Hemoglobin within 2 days after OR (g/L) (including day of OR) [Derived by Innovian]**	Patient	Jan 1, 2013 to Dec 1, 2017	As this may affect outcomes, it will be included as a covariate.

<table>
<tr><td>Innovian</td><td>PRBC: Red Blood Cell transfusion (mL)</td><td>Patient</td><td>Jan 1, 2013 to Dec 1, 2017</td><td>As this may affect outcomes, it will be included as a covariate.</td></tr>
<tr><td>Innovian</td><td>Surgical APGAR Score [Derived by Innovian based on variables already requested]</td><td>Patient</td><td>Jan 1, 2013 to Dec 1, 2017</td><td>
<table>
<tr><th></th><th>0 points</th><th>1 point</th><th>2 points</th><th>3 points</th><th>4 points</th></tr>
<tr><td>Estimated blood loss (mL)</td><td>> 1,000</td><td>601−1,000</td><td>101−600</td><td>≤ 100</td></tr>
<tr><td>Lowest mean arterial pressure (mmHg)</td><td>< 40</td><td>40−54</td><td>55−69</td><td>≥ 70</td></tr>
<tr><td>Lowest heart rate (beats/min)</td><td>> 85</td><td>76−85</td><td>66−75</td><td>56−65</td></tr>
</table>
Surgical score (0-10) = sum of all points
The Surgical APGAR Score is an existing, validated method of risk stratification at the end of surgery, and will be compared to the machine learning models.</td></tr>
<tr><td colspan="5">Mortality</td></tr>
<tr><td>Vital Statistics</td><td>Mortality (30-day all cause)

[Derived by HDNS based on DOD from Vital Statistics]</td><td>Patient</td><td>Jan 1, 2013 to Dec 31, 2017</td><td>Binary outcome (yes/no), derived from DOD within 30 days from PDATE. This is needed to compute 30-day all-cause mortality. Primary outcome for the study to be used for modeling.</td></tr>
<tr><td>CIHI DAD</td><td>OPDEATH: operative death</td><td>Patient</td><td>Jan 1, 2013 to Dec 31, 2017</td><td>OPDEATH will be described in descriptive statistics.

1 = Died in Operating Room

2 = Did Not Die in Operating Room</td></tr>
<tr><td>Vital Statistics</td><td>DOD: Date of death</td><td>Patient</td><td>Jan 1, 2013 to Dec 31, 2017</td><td>For internal use by HDNS to compute 30-day all-cause mortality (primary outcome), and the Number of</td></tr>
</table>

				postoperative day of death (i.e. Date of death minus PDATE).
CIHI DAD	**Number of postoperative day of death** [Derived by HDNS based on DOD from Vital Statistics]	Patient	Jan 1, 2013 to Dec 31, 2017	Derived discrete (n = 1, 2, 3… 30) variable, of the patients with 30-day mortality = yes. This variable is defined as DOD [if ≤30 days after PDATE] minus PDATE. Survival statistics will be performed (% vs. postoperative day)
CIHI DAD	**In-hospital death** [Derived by HDNS based on "DISCHARGE: Discharge disposition"]	Patients	Jan 1, 2013 to Dec 31, 2017	Derived binary variable (yes/no). Of those who died within 30 days after surgery, descriptive statistics will be performed for in-hospital vs. out-of-hospital mortality (yes/no) "Yes" if DISCHARGE = 7 or 8: 7 = Died 8 = Cadaver donor admitted for organ/tissue retrieval Else = "no"
Vital Statistics	**UCAUSE:** Underlying Cause of Death	Patient who died within 30 days after surgery	Jan 1, 2013 to Dec 31, 2017	For patients who died within 30 days of surgery, we are interested in the cause of death. The UCAUSE will only be used internally by HDNS to create flags for these causes of death as categorized according to ICD codes as follows: acute myocardial infarction (I21 to I22, I24), cardiac arrest (I46.0, 146.1, I46.9), ventricular tachycardia (I47.2), shock (R57, T81.1) excluding septic shock (R57.2), congestive heart failure (I50.0, I50.1, I50.9), pulmonary edema (J81), complete heart block (I44.2), pneumonia (J13 to J18, J69.0, J69.8, J95.4), pulmonary embolism (I26), acute respiratory failure (J95.1, J95.2,

				J96.0), respiratory arrest (R9.2), strokes and transient ischemic attacks (I60 to I69, G45), Delirium (F05), Acute kidney injury (N17), Septic shock (R57.2) Causes not fitting the above secondary outcomes will be categorized according to standard ICD categories: Infectious diseases (A00-B99) Neoplasm (C00-D48) Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89) Endocrine, nutritional and metabolic diseases (E00-E90) Mental and behavioural disorders (F00-F99) Diseases of the nervous system (G00-G99) Diseases of the circulatory system (I00-I99) Diseases of the respiratory system (J00-J99) Diseases of the digestive system (K00-K93) Diseases of the skin and subcutaneous tissue (L00-L99) Diseases of the musculoskeletal system and connective tissue (M00-M99) Diseases of the genitourinary system (N00-N99) Pregnancy, childbirth and the puerperium (O00-O99) Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)

				Injury, poisoning and certain other consequences of external causes (S00-T98) External causes of morbidity and mortality (V01-Y98) Causes not fitting any of the above categories will be coded as UCAUSE = other Descriptive statistics will be performed for causes.
Vital Statistics	**All causes of death (case 1-13)**	Patient who died within 30 days after surgery	Jan 1, 2013 to Dec 31, 2017	For patients who died within 30 days of surgery, we are interested in the cause(s) of death. However, since the UCAUSE may be missing or not reflect the whole picture, we would also like to request all causes of death. This will only be used internally by HDNS to create flag(s) for these causes of death as categorized according to ICD codes as follows (note that each patient may have multiple flags): acute myocardial infarction (I21 to I22, I24), cardiac arrest (I46.0, 146.1, I46.9), ventricular tachycardia (I47.2), shock (R57, T81.1) excluding septic shock (R57.2), congestive heart failure (I50.0, I50.1, I50.9), pulmonary edema (J81), complete heart block (I44.2), pneumonia (J13 to J18, J69.0, J69.8, J95.4), pulmonary embolism (I26), acute respiratory failure (J95.1, J95.2, J96.0), respiratory arrest (R9.2), strokes and transient ischemic attacks (I60 to I69, G45), Delirium (F05), Acute kidney injury (N17), Septic shock (R57.2)

				Causes not fitting the above secondary outcomes will be categorized according to standard ICD categories: Infectious diseases (A00-B99) Neoplasm (C00-D48) Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89) Endocrine, nutritional and metabolic diseases (E00-E90) Mental and behavioural disorders (F00-F99) Diseases of the nervous system (G00-G99) Diseases of the circulatory system (I00-I99) Diseases of the respiratory system (J00-J99) Diseases of the digestive system (K00-K93) Diseases of the skin and subcutaneous tissue (L00-L99) Diseases of the musculoskeletal system and connective tissue (M00-M99) Diseases of the genitourinary system (N00-N99) Pregnancy, childbirth and the puerperium (O00-O99) Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99) Injury, poisoning and certain other consequences of external causes (S00-T98) External causes of morbidity and mortality (V01-Y98)

				Causes not fitting any of the above categories will be coded as UCAUSE = other Descriptive statistics will be performed for causes.
Additional Postoperative Morbidity (in addition to DXCODE above)				
CIHI DAD	**FLAG_HEARTRESUS:** Heart Resuscitation Flag	Patient	Jan 1, 2013 to Dec 31, 2017	Part of secondary outcomes to be included into model. Descriptive statistics will be performed for this subcategory, within the category of cardiac complications, and an overall composite measure of each category. 0 = No 1 = Yes
CIHI DAD	**FLAG_MECHVEN_GE96:** Mechanical Ventilation ≥ 96 hours	Patient	Jan 1, 2013 to Dec 31, 2017	Part of secondary outcomes to be included into model. Descriptive statistics will be performed for this subcategory, within the category of respiratory complications, and an overall composite measure of each category. 0 = No 1 = Yes
CIHI DAD	**Composite morbidity** [Derived by HDNS]	Patient	Jan 1, 2013 to Dec 31, 2017	Binary variable (yes/no) derived based on any of the following: FLAG_HEARTRESUS, FLAG_MECHVEN_GE96, or ICD code of any of: acute myocardial infarction (I21 to I22, I24), cardiac arrest (I46.0, 146.1, I46.9), ventricular tachycardia (I47.2), shock (R57, T81.1) excluding septic shock (R57.2), congestive heart failure (I50.0, I50.1, I50.9), pulmonary edema (J81), complete heart block (I44.2), pneumonia (J13 to J18, J69.0, J69.8, J95.4), pulmonary embolism (I26), acute respiratory failure (J95.1, J95.2, J96.0), respiratory arrest (R9.2), strokes and transient ischemic attacks (I60 to I69,

				G45), Delirium (F05), Acute kidney injury (N17), Septic shock (R57.2) Part of secondary outcomes to be included into model. Descriptive statistics will be performed.
CIHI DAD	**ICU admission** [Derived by HDNS] **SCUNUM[1-n]:** Special Care Unit Num "The SCU Unit Number is a code identifying the type of special care unit where the patient receives critical care." [Derived by HDNS]	Patient	Jan 1, 2013 to Dec 31, 2017	Two variables to be derived: 1. Preoperative ICU (yes/no) 2. Postoperative ICU (yes/no) Preoperative ICU admission (yes/no) is a covariate to be included into the model. Postoperative ICU admission (yes/no) is a secondary outcome to be included into model. Descriptive statistics will be performed. Derivation process: ICU = yes include the following SCUNUM: 10 = Medical Intensive Care Nursing Unit 20 = Surgical Intensive Care Nursing Unit 25 = Trauma Intensive Care Nursing Unit 30 = Combined Medical/Surgical Intensive Care Nursing Unit 35 = Burn Intensive Care Nursing Unit 40 = Cardiac Intensive Care Nursing Unit Surgery 45 = Coronary Intensive Care Nursing Unit 80 = Respirology Intensive Care Nursing Unit Else ICU = no If the SCU Admit Date is on or before PDATE, then it would be defined as Preoperative AND postoperative ICU admission. Else, postoperative ICU admission only.

CIHI DAD	**READMIT:** Readmission Code (within 30 days after PDATE) [Derived by HDNS]	Patient	Jan 1, 2013 to Dec 31, 2017	Readmission within 30 days of PDATE (yes/no) is a secondary outcome to be included into model. Descriptive statistics will be performed. Derived: Postoperative readmission = yes include the following: 1 = Planned readmission from previous acute care 2 = Unplanned readmission within 7 days following discharge from acute care 3 = Unplanned readmission 8 – 28 days following discharge from acute care 4 = <=7 days, unplanned 5 = New patient 9 = None of the above. Else Postoperative readmission = no
CIHI DAD	**LOS:ELOS** Ratio of Length of Stay (LOS) to Expected Length of Stay (ELOS) as assigned by the Case Mix Grouping [Derived by HDNS]	Patient	Jan 1, 2013 to Dec 31, 2017	This will be dichotomized by HDNS: LOS:ELOS >1 (yes/no). This is a secondary outcome to be included into model. Descriptive statistics will be performed.